art. An overview of patent information in biotechnology and a survey of relevant sources of patent information useful for retrospective searching and for current awareness is given in Berks, TIBTECH 12 (1994), 352-364.

REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

As correctly indicated in the Office Action Summary, claims 24-45 are presently pending in this application.

By the present amendment, the specification has been amended at page 16, lines 20-32, to remove reference to the embedded hyperlinks and/or brower-executable codes. Support for this amendment can be found at least in the original specification at this location. Accordingly, no new matter is believed to have been added.

Objection to the Specification

Citing M.P.E.P. § 608.01, the Examiner objected to the specification because the paragraph at page 16, lines 20-32, contained embedded hyperlinks and/or other form of brower-executable codes. Applicants submit that the present amendment removes reference to the embedded hyperlinks and/or brower-executable codes. Therefore, the Examiner's rejection has been rendered moot.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 24-45 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Official Action, Paper No. 11, pages 2-7. In particular, the Examiner has alleged the following: (1) the claimed invention falls within the realm of gene therapy: (2) gene therapy is a highly unpredictable art; (3) multiple sclerosis is a chronic, incurable disease; (4) there is no art recognized nexus between the results in the mouse models and the results which one skilled in the art would reasonably expect to observe in humans; (5) the specification fails to address any secretory signal sequence or transfecting facilitating vehicle that could be used in an expression vector to reach a therapeutic level of beta interferon in humans; and (6) there is no correlation between vectors, routes of delivery, dosage amounts that correlate to the treatment of multiple sclerosis. Official Action, Paper No. 11, pages 5-6. Applicants respectfully traverse this rejection.

Applicant submits that the specification is fully enabled for the claimed invention for at least the following reasons. First, the specification describes the prior art use of recombinant beta-interferon (hereinafter "INF-β") for the treatment of multiple sclerosis (hereinafter "MS"). Specification, page 2. The specification even teaches that at least one recombinant INF-β product, Betaseron™ has been approved by the Food and Drug Administration (hereinafter "FDA") for MS therapy. These treatments consist in administering recombinant INF β, either subcutaneously (the dosage is usually 0.25 mg ($8x10^6$ IU) of recombinant INF-β injected every day) or intramuscularly ($6x10^6$ IU β-INF-

1b injected weekly). Furthermore, the specification teaches that the administration of recombinant INF-β reduces the frequency and intensity of clinical exacerbations and delays the progression of the disability. Specification, pages 2-3. Nonetheless, the specification recognizes the deficiencies of the prior art methods of administration exogenous recombinant interferon proteins. These deficiencies include undesirable systemic side-effects, such as erythrematous reactions at the injection-site, flu-like symptoms, and reduced efficacy resulting from development of neutralizing antibodies to the exogenous protein. Despite these deficiencies, the art, (including the FDA) recognizes the use of INF-β as an effective treatment for MS patients.

Applicant's claimed invention solves the above-described prior art deficiencies. To this end, Applicant surprisingly discovered that nucleic acid capable of expressing INF-β when injected into mammals suffering from an immune disease induces a sustained and unexpected improvement of the health of the treated mammal when compared to untreated mammals. Specification, pages 21-22; Figure 2. Example 2 demonstrates the detection of human INF-β in the blood of mice long after injection with the claimed invention. Specification, page 23. Furthermore, the specification provides animal models demonstrating the efficacy of the claimed invention. Mice suffering from experimental autoimmune encephalomyelitis (hereinafter "EAE") were effectively treated by intramuscular injections of INF-β plasmid. Specification, pages 23-27; Figures 3-5. A fifty day follow-up after immunization revealed that animals treated with INF-β plasmids showed no signs of clinical EAE, whereas non-treated animals displayed symptoms of EAE.

Applicant notes that EAE is the art recognized animal model of MS. Applicants hereby submit the enclosed copy of Trevor Owens, *Multiple Sclerosis: The Immunology of Multiple Sclerosis and Its Animal Model Experimental Allergic Encephalomyelitis*, NEUROLOGIC CLINICS 13(1): 51-73 (1995) (hereinafter "Owens") as evidence that EAE is the art recognized model for autoimmune disease and MS. According to this review article, "EAE is the best available model for the inflammatory processes that occur in MS, and for the disease process." Owens at 66. Based on this reference, it is clear that those skilled in the art recognize that EAE is the animal model for MS.

Applicant further notes that gene therapy is a plausible treatment for MS. To this end, Applicant hereby submits the enclosed copy of the abstract for Ruffini et al., *Fibroblast growth factor-II gene therapy reverts the clinical course and the pathological signs of chronic experimental autoimmune encephalomyelitis in C57BL/6 mice*, GENE THERAPY 8(16):1207-13 (2001) (hereinafter "Ruffini"). Ruffini teaches that injections of HSV-1-derived vector coding for the fibroblast growth factor-II (hereinafter "FGF-II") effectively reduces disease symptoms in mice suffering from EAE, the animal model for MS. See Ruffini, abstract. Ruffini suggests that gene therapy represents an useful tool for the treatment of MS.

Furthermore, it is well established that an *in vitro* or *in vivo* animal model example in the specification constitutes a "working example" if the art recognizes a particular model as correlating to a specific condition. In re Brana, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications); M.P.E.P. § 2164.02. Applicants submit that the

prior art references support the notion that the *in vitro* and *in vivo* animal models provided in the specification correlate to an immune disease, such as MS.

Thus, upon reading the teachings of the specification and upon being aware of the knowledge in the art, it is clear that the claimed invention prevents clinical signs of EAE, which is the art recognized animal model equivalent of MS. It logically follows then that the specification demonstrates the efficacy of the claimed invention as an alternative treatment for MS in humans. Such evidence refutes the Examiner's assertion that there is no art recognized "nexus" between the disclosed results in the EAE mouse model and the results which the skilled artisan would reasonably expect to observe in humans. When taken in view with the FDA's prior approval of exogenous INF-β therapy of MS, one skilled in the art would clearly recognize the use of claimed invention for the treatment of an immune disease, especially MS. Such evidence cannot be summarily dismissed.

As to the Examiner's contention that the specification fails to provide guidance as to the route of administration and dosage, Applicant submits that the specification clearly provides the requisite guidance necessary to enable the claimed invention. To this end, the specification at pages 11-12 teaches that the pharmaceutical composition can be administered by any suitable art recognized route of administration, such as intradermal, subdermal, intravenous, intramuscular, intranasal, intracerebral, intratracheal, intraarterial, intraperitoneal, intravesical, intrapleural, intracoronary, intratumoral, or transdermal. Moreover, as discussed above, the specification demonstrates an effective dosage of *in vivo* transmuscular injection of plasmid DNA in mice. The specification at pages 11-12 also provides the concentration of the nucleic acid in the pharmaceutical composition, as well as

the recommended dosages in humans. Thus, based upon the teachings and examples in the specification, one of skill in the art would easily be able to extrapolate the recommended dosages for human use without undue experimentation. Applicants remind the Examiner that a considerable amount of experimentation is permissible and may not be considered undue if the skilled artisan is given sufficient direction or guidance. In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); M.P.E.P. § 2164.04. The specification clearly provides the requisite direction and guidance.

Lastly, the Examiner's allegation regarding gene therapy vectors, secretory signal sequences, and transfection-facilitating vehicles is misplaced. Applicants submit that even the PTO has recognized that vectors encoding lymphokines are enabled as a recognizable form of gene therapy. See Felgner et al. (US 5,580,859) (hereinafter "Felgner"), columns 13-16, 27-28, and claim 16; Nabel et al. (US. 5,707,969) (hereinafter "Nabel"), claim 9. Felgner and Nabel teach the construction of numerous such gene therapy vectors containing the sequence encoding INF-β. Applicant also submits that the instant specification at pages 7-11 and 18-19 provides numerous examples of vectors and secretory sequences. The specification also provides numerous examples of transfection-facilitating vehicles. The specification even indicates that such vehicle are readily known and available in the art. Specification page 10, line 20 to page 11, line 11. Applicant notes that "a specification need not teach, and preferably omits, what is well known in the art." In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); M.P.E.P. § 2164.01.

Therefore, in view of the above, Applicant submits that one of skill in the art upon reading the specification and upon being aware of the knowledge in the art would be able

to practice the claimed invention without undue experimentation. Thus, the Examiner is respectfully requested to withdraw the rejection.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or to the application in general, the Examiner is invited to telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____

Jay F. Williams
Registration No. 48,036

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: May 15, 2002

ATTACHMENT TO AMENDMENT AND REPLY

Marked-up Copy

Paragraph on page 16, lines 20-32

([bracketed] items deleted; underlined items added)

These and other embodiments are disclosed or are obvious from and encompassed by the description and examples of the present invention. Further literature concerning any one of the methods, uses and compounds to be employed in accordance with the present invention may be retrieved from public libraries, using for example electronic devices. For example the public database "Medline" may be utilized which is available on the Internet[, e.g. under http://www.ncbi.nlm.nih. gov/PubMed/medline.html]. Further databases and Internet addresses[, such as http://www.ncbi.nlm.nih.gov, http://www.infobiogen.fr, http://www.fmi.ch/biology/research_tools.html, http://www.tigr.org,] are known to the person skilled in the art [and can also be obtained using, e.g., http://www.lycos.com]. An overview of patent information in biotechnology and a survey of relevant sources of patent information useful for retrospective searching and for current awareness is given in Berks, TIBTECH 12 (1994), 352-364.